

REVIEW ARTICLE

Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases

Jan H.M.B. Stoot^{1,2}, Robert J.S. Coelen^{1,2}, Mechteld C. de Jong¹ & Cornelis H.C. Dejong^{1,3}

¹Department of Surgery, Maastricht University Medical Centre, ²Department of Surgery, Orbis Medical Centre, Sittard, and ³Maastricht University, Nutrim School for Nutrition, Toxicology and Metabolism, Maastricht, the Netherlands

Abstract

Background: Malignant transformation of hepatocellular adenomas (HCAs) into hepatocellular carcinomas (HCCs) has been reported repeatedly and is considered to be one of the main reasons for surgical treatment. However, its actual risk is currently unknown.

Objective: To provide an estimation of the frequency of malignant transformation of HCAs and to discuss its clinical implications.

Methods: A systematic literature search was conducted using the following databases: The Cochrane Hepatobiliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE and EMBASE.

Results: One hundred and fifty-seven relevant series and 17 case reports (a total of 1635 HCAs) were retrieved, reporting an overall frequency of malignant transformation of 4.2%. Only three cases (4.4%) of malignant alteration were reported in a tumour smaller than 5 cm in diameter.

Discussion: Malignant transformation of HCAs into HCCs remains a rare phenomenon with a reported frequency of 4.2%. A better selection of exactly those patients presenting with an HCA with an amplified risk of malignant degeneration is advocated in order to reduce the number of liver resections and thus reducing the operative risk for these predominantly young patients. The Bordeaux adenoma tumour markers are a promising method of identifying these high-risk adenomas.

Keywords

hepatocellular adenoma, liver adenoma, malignant transformation, hepatic adenoma, frequency, hepatocellular carcinomas

Received 10 May 2010; accepted 12 July 2010

Correspondence

Jan H.M.B. Stoot, Department of Surgery, Maastricht University Medical Centre, P. Debyelaan 25, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. Tel: +31 43 387 5481; Fax: +31 43 387 5473; E-mail: jan@stoot.com

Introduction

Hepatocellular adenomas (HCAs) are uncommon and essentially benign tumours in the liver that occur predominantly, but not exclusively, in young women taking oral contraceptives (OCs).^{1,2} HCAs are caused by benign proliferation of hepatocytes with high glycogen and fat content but lack normal hepatic architecture.

This paper was presented at the International Hepato-Pancreato-Biliary Association Meeting, 18–22 April 2010, Buenos Aires, Argentina.

They usually present as a solitary nodule that may reach up to 30 cm in diameter.

Clinical manifestations range from asymptomatic presentation or abdominal pain localized to the epigastric region or right upper quadrant to a palpable liver mass or even life-threatening haemorrhage in the case of rupture.^{3,4} However, these tumours are most often encountered as an incidental finding during imaging for unrelated pathology.

Although the exact pathogenetic mechanism of the development of HCAs remains unknown, an association between

formation of HCAs and the use of OCs or androgen-containing anabolic steroids is assumed.⁵⁻⁷ Studies from the past century suggest that long-term use of OCs increases the annual incidence of HCAs from 1 per million to 3 to 4 per 100 000.^{1,8} In addition, OCs and androgen-containing steroid anabolics have also been suggested to increase the number and size of these adenomas. Conversely, HCAs may show signs of regression on discontinuance of OC use.^{9,10} HCAs are further reported to be associated with type I and type III glycogen storage disease (GSD) and, furthermore, are more likely to be multifocal or to become malignant in these patients.¹¹

The most important complications of HCAs are haemorrhage and malignant transformation into hepatocellular carcinomas (HCCs). Thus, these are the two main reasons for surgical treatment. However, little is known about the true incidence, associated risk factors and the aetiology of malignant alteration of HCAs. The aim of the current systematic review is to provide an estimation of the frequency of this phenomenon by means of a systematic literature search and, moreover, to discuss the clinical implications.

Methods

Search strategy

A search of all literature up to February 2010 was performed independently by two investigators (J.H.M.B.S. and R.J.S.C.) employing all relevant databases including the MEDLINE, PubMed and EMBASE databases, The Cochrane Hepatobiliary Group Controlled Trials Register and The Cochrane Central Register of Controlled Trials (CENTRAL). Keywords were 'hepatocellular adenoma', 'benign liver tumours', 'malignant transformation' and 'liver resection'. The search was limited to studies restricted to humans and articles published from 1970 onwards. This time period was chosen as the number of reports on hepatocellular adenomas began rising in the 1970s. All titles and abstracts were screened and relevant articles were selected.

Study selection criteria

Studies were included if they described a series of patients with HCAs undergoing surgery, embolization or other (conservative) treatment. Case reports and imaging studies of these benign lesions were also included. Only those studies containing a definite histological diagnosis of the tumours were included. Studies concerning HCAs in patients with GSD were excluded as these patients carry a higher risk of developing these lesions and, moreover, are thought to have an increased risk of malignant degeneration. Furthermore, patients with adenomatosis (more than 10 HCAs) were excluded, as this is considered as a different entity.^{12,13} No further formal quality assessment or selection criteria were employed.

Data extraction

The reference lists of retrieved articles were reviewed for potentially relevant studies and case reports were also reviewed. When

the full text of an article was not available, an Inter Library Loan account was used to retrieve these articles from national libraries. All data of selected articles were screened for duplicate adenoma cases that had already been reported in prior studies. In the case of an overlapping series, only the most recent or complete publication was included. The corresponding author of relevant studies identified from the initial search, together with experts in the field, were contacted for any information on unpublished articles and in case of need for clarification.

Outcome measures and statistical analysis

The main outcome measure was the rate of malignant transformation. In addition, the numbers of (resected) HCAs, the number of females, mean age at presentation, mean diameter of the lesion, OC use and presence of haemorrhage were all assessed. All reported adenoma cases were listed in a table. All data were presented as mean or median values and percentages.

Results

A total of 3935 articles were identified through the electronic searches of PubMed ($n = 120$), The Cochrane Hepatobiliary Group Controlled Trials Register and CENTRAL in the Cochrane Library ($n = 12$) and a combined Ovid MEDLINE and EMBASE search ($n = 3803$). Through reading titles and abstracts 1196 duplicates as well as 2658 noticeably irrelevant articles and eight articles on GSD or adenomatosis were excluded. Furthermore, four articles were excluded as they contained a series of adenomas that had been previously reported. Altogether, 69 articles were selected for more detailed evaluation. From this analysis, a further 108 studies were included through cross-referencing and three studies were excluded because of a previously reported series of adenomas. In total, 174 articles (157 series and 17 case reports) on liver surgery and imaging, including case series of HCA, were retrieved (Fig. 1).

Hepatocellular adenoma series in the literature

The 157 series contained a total of 1617 HCAs worldwide, of which 1445 HCAs (89%) were resected (Table 1). Thirty-six patients with adenomatosis and 14 patients with GSD were excluded from a total of eight studies. There were 51 series that contained only a single patient with HCA. Most of these reports were published in the 1970s when individual cases of HCA in women using OCs were regularly reported. The three largest series contained 91,¹⁴ 124¹⁵ and 128¹⁶ HCAs, respectively (patients having adenomatosis or GSD not included).

Case reports on malignant transformation of hepatocellular adenomas

The literature search identified 17 case reports concerning malignant transformation (a total of 19 cases), which are presented in Table 2. The mean age of these patients at the time of surgery was 41 years (range, 19 to 70). Five of these patients (26%) were men,

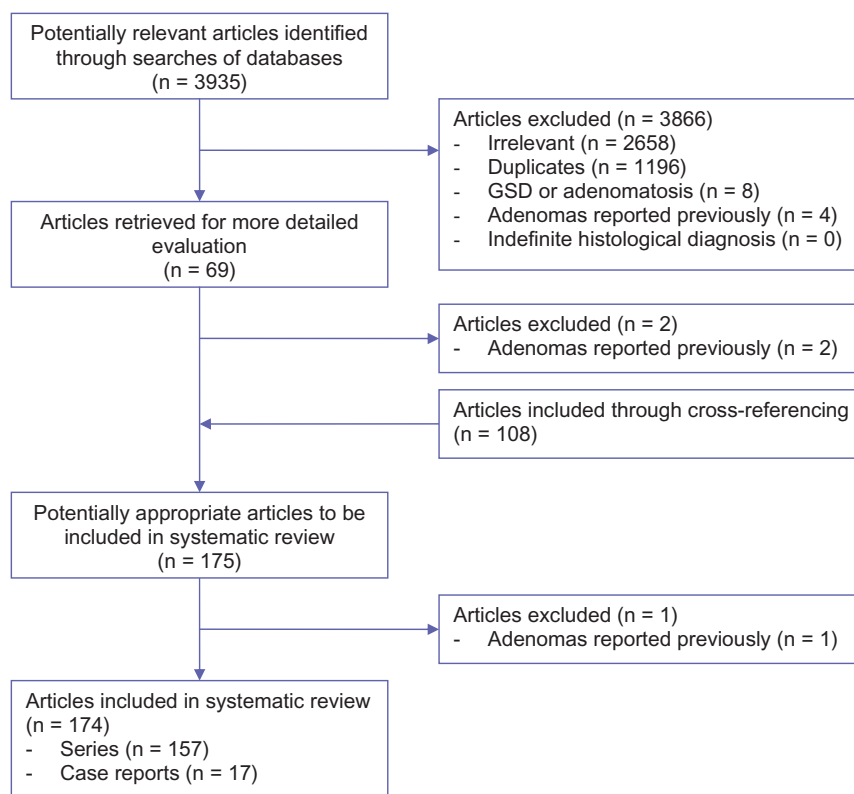


Figure 1 Flowchart literature search. GSD, glycogen storage disease

of whom one had a history of oral prednisolone use and another had a history of anabolic steroid use.^{17,18} Twelve of the 14 women reported to have malignant alteration of an HCA presented with a history of OC usage. The mean time elapsed between commencement of OC therapy and diagnosis of HCA was 14 years. Most cases of malignant transformation of HCAs were seen at the time of the diagnosis of HCA. Furthermore, only three cases (16%) among these 19 cases of malignant degeneration presented with multiple HCAs^{19–21} and six cases (32%) were complicated by haemorrhage.^{21–26}

Although some authors noted that HCAs may regress on discontinuation of oral contraceptive use,^{9,10,22} three case reports suggested that even after discontinuation of OC use, HCC can still develop irrespective of the occurrence of regression of the HCA.^{20,22,26} Moreover, the reports by Chuang *et al.*¹⁷ and Colovic *et al.*²⁷ showed that malignant transformation of HCAs can occur in patients without a history of OC use.

Frequency of malignant transformation of hepatocellular adenomas in the literature

Out of the 1617 HCAs listed in Table 1, 50 tumours (3.1%) underwent malignant transformation into HCC. By combining these data with the case reports aforementioned (Table 2), an estimation of the exact frequency of malignant alteration of HCAs could

be made, as the data showed that 68 of a total of 1635 (4.2%) HCAs underwent malignant transformation. Moreover, of all resected HCAs (1462 in total), 4.5% contained focal malignancy. Although not the main scope of the current review, haemorrhage was found in 406 out of 1635 (25%) tumours, in keeping with literature data.^{13,14,28}

Association between size of HCA and risk of malignant transformation

The size of HCA has, by current consensus, remained the main decision criterion in determining whether or not resection is indicated, based upon the observation that intratumoral bleeding only seldom takes place in lesions smaller than 5 cm.^{2,15,29} Concordant to this observation, most of the resected adenomas identified in the current search were resected after they reached a minimal size of 5 cm.^{4,30} However, limited data was hitherto reported concerning the possibility of an association between the size of HCAs and the risk of malignant transformation. Particularly, no specific studies on this subject have been conducted and, moreover, most series in the literature did not report precise measurements of the tumours. Nonetheless, some case reports and series of HCAs with particular diameters were reported. Deneve *et al.*¹⁵ analysed 124 patients with an HCA, of which five cases contained signs of malignant alteration. The mean size of these five tumours was

Table 1 Overview of series of hepatocellular adenomas with or without malignant transformation into hepatocellular carcinomas

Study	Year	HCA (n)	Resected (n)	HCC (n)	Female (n)	Mean age (y)	Mean diameter (cm)	OC use (n)	Haemorrhage (n)	Embolization (n)	Smallest diameter (cm) ^a
Malt <i>et al.</i> ⁵⁹	1970	4	3	0	3	–	15.8	–	1	0	
Kay and Schatzki ⁶⁰	1971	1	0	0	1	26	10	–	0	0	
Horvath <i>et al.</i> ⁶¹	1972	1	1	0	1	28	15	1	0	0	
Motsay and Gamble ⁶²	1972	5	5	0	5	30.2	9.6	–	1	0	
Baum <i>et al.</i> ⁶³	1973	7	7	0	7	–	–	7	2	0	
Contostavlos ⁶⁴	1973	1	0	0	1	37	15	1	1	0	
Davis <i>et al.</i> ⁶⁵	1973	3	3	0	3	25	–	–	3	0	
Hermann and David ⁶⁶	1973	1	1	0	1	20	12	–	1	0	
Albritton <i>et al.</i> ⁶⁷	1974	4	4	0	4	32.8	–	–	0	0	
Berg <i>et al.</i> ⁶⁸	1974	4	1	0	4	26.5	–	3	3	0	
Kelso ⁶⁹	1974	1	1	0	1	36	–	1	1	0	
Knapp and Ruebner ⁷⁰	1974	1	1	0	1	33	17	1	1	0	
Tountas <i>et al.</i> ⁷¹	1974	1	1	0	1	30	–	1	1	0	
Ameriks <i>et al.</i> ⁷²	1975	8	8	0	8	34	15	8	3	0	
Antoniades <i>et al.</i> ⁷³	1975	1	1	0	1	32	10.8	1	1	0	
Antoniades and Brooks ⁷⁴	1975	1	1	0	1	30	6.5	1	1	0	
Galloway <i>et al.</i> ⁷⁵	1975	4	1	0	4	41.5	–	1	2	0	
Model <i>et al.</i> ⁷⁶	1975	1	1	0	1	31	2.5	1	1	0	
Nissen and Kent ⁷⁷	1975	1	1	0	1	27	–	1	1	0	
Stenwig and Solgaard ⁷⁸	1975	1	1	0	1	1	31	10	1	1	
Ammentorp and Carson ⁷⁹	1976	4	4	0	4	28.8	–	4	0	0	
Andersen and Packer ⁸⁰	1976	1	1	0	1	24	4.5	1	1	0	
Baek <i>et al.</i> ⁸¹	1976	1	1	0	1	31	18	1	1	0	
Brander <i>et al.</i> ⁸²	1976	1	0	0	1	24	–	1	1	0	
Edmondson <i>et al.</i> ⁵	1976	42	41	0	42	–	–	34	29	0	
Lansing <i>et al.</i> ⁸³	1976	3	3	0	2	33.7	8.7	1	1	0	
Sears <i>et al.</i> ⁸⁴	1976	1	1	0	1	26	10	1	1	0	
Chan and Detmer ⁸⁵	1977	4	4	0	4	35.3	11.3	4	2	0	
Fechner ⁸⁶	1977	6	5	0	6	30.2	–	5	3	0	
Fortner <i>et al.</i> ⁸⁷	1978	1	1	0	–	–	–	–	–	0	
Gold <i>et al.</i> ⁸⁸	1978	12	7	0	7	30	6.8	6	1	0	
Ramseur and Cooper ⁸⁹	1978	1	1	0	1	26	8	1	0	0	
Bird <i>et al.</i> ⁹⁰	1979	1	1	0	1	39	15	1	1	0	
Cady <i>et al.</i> ⁹¹	1979	1	1	0	–	–	–	–	–	0	
Catalano <i>et al.</i> ⁹²	1979	4	4	0	4	29	–	4	0	0	
Mariani <i>et al.</i> ⁴¹	1979	1	1	0	1	27	8.5	1	1	0	
Wheeler <i>et al.</i> ⁹³	1979	1	0	0	1	–	–	1	0	1	
Weil <i>et al.</i> ⁹⁴	1979	8	8	0	7	24	–	4	4	0	
Kelly ⁹⁵	1980	2	1	0	2	30	–	2	1	0	
Neuberger <i>et al.</i> ⁹⁶	1980	3	2	1	3	35	–	3	0	0	–
Herczeg <i>et al.</i> ⁹⁷	1981	1	1	0	1	36	–	1	1	0	
Isman <i>et al.</i> ⁹⁸	1981	2	2	0	0	41	–	–	2	0	
Thompson and Little ⁹⁹	1981	1	1	0	1	30	9	1	0	0	
Bühler <i>et al.</i> ⁹	1982	3	0	0	3	30.3	6.7	3	1	0	
Kerlin <i>et al.</i> ¹⁰⁰	1983	23	17	2	21	34	9	17	16	0	–
Meensook and Sirisabya ¹⁰¹	1983	1	1	0	1	25	16	1	1	0	
Thompson <i>et al.</i> ¹⁰²	1983	5	5	0	5	32	–	2	2	0	
Cassinelli ¹⁰³	1985	1	1	0	1	38	–	1	0	0	
Gonzalez and Marks ¹⁰⁴	1985	12	12	0	–	–	–	–	2	0	
Welch <i>et al.</i> ¹⁰⁵	1985	13	12	0	12	31	11	9	11	0	
Mathieu <i>et al.</i> ¹⁰⁶	1986	27	27	0	27	34	7.5	26	5	0	
Creagh <i>et al.</i> ¹⁰⁷	1988	1	1	0	0	27	4	1	1	0	

Table 1 Continued

Study	Year	HCA (n)	Resected (n)	HCC (n)	Female (n)	Mean age (y)	Mean diameter (cm)	OC use (n)	Haemorrhage (n)	Embolization (n)	Smallest diameter (cm) ^a
Leese <i>et al.</i> ²	1988	18	17	0	15	33	13	11	9	4	
Marks <i>et al.</i> ⁴²	1988	3	3	0	3	35.7	–	3	1	0	
Ringe <i>et al.</i> ¹⁰⁸	1989	5	4	0	4	34	10	–	1	0	
Flowers <i>et al.</i> ¹⁰⁹	1990	6	6	0	5	28.8	7.3	5	6	0	–
Iwatsuki <i>et al.</i> ¹¹⁰	1990	25	25	0	20	31	12	12	4	0	
Leborgne <i>et al.</i> ¹¹¹	1990	2	0	0	2	28	14	2	2	1	
Tao ⁴⁷	1991	9	7	0	9	33.5	–	9	0	0	–
Belghiti <i>et al.</i> ¹¹²	1993	12	12	1	12	33	9.2	11	6	0	–
Arrivé <i>et al.</i> ¹¹³	1994	29	21	3	27	37.4	5.4	24	15	0	–
Eckhauser <i>et al.</i> ¹¹⁴	1994	8	8	0	8	31.5	9.5	7	0	0	
Foster and Berman ¹⁹	1994	13	–	1	12	–	–	–	1	0	12
Golli <i>et al.</i> ¹¹⁵	1994	8	8	0	7	30	6.8	6	1	0	
Paineau <i>et al.</i> ¹¹⁶	1994	1	1	0	0	–	–	0	0	0	
Paulson <i>et al.</i> ¹¹⁷	1994	9	6	0	8	–	–	6	–	0	
Pertschy <i>et al.</i> ¹¹⁸	1994	30	29	0	–	–	–	–	0	0	
Cherqui ¹¹⁹	1995	6	6	0	6	32	7.8	5	3	0	
Chung <i>et al.</i> ¹¹⁰	1995	16	15	0	14	34.6	5.4	5	12	0	
Cuesta <i>et al.</i> ¹²⁰	1995	1	1	0	1	56	6	–	0	0	
Ferzli <i>et al.</i> ¹²¹	1995	1	1	0	1	43	9	–	–	0	
Nagorney ¹²²	1995	24	19	1	22	35	9	9	4	0	–
Ault <i>et al.</i> ²⁹	1996	11	4	3	10	37.6	–	9	4	4	5.5
Azagra <i>et al.</i> ¹²³	1996	1	1	0	1	42	6	–	0	0	
Cheng <i>et al.</i> ¹²⁴	1996	1	1	0	1	39	6.4	1	1	0	
Kelly <i>et al.</i> ¹²⁵	1996	9	9	0	–	–	–	–	0	0	
Vogl <i>et al.</i> ¹²⁶	1996	1	0	0	1	27	–	–	0	0	
De Carlis <i>et al.</i> ¹²⁷	1997	19	19	2	19	31.8	7.9	17	5	0	–
Krug <i>et al.</i> ¹²⁸	1997	8	8	0	–	–	–	–	–	0	
Weimann <i>et al.</i> ¹²⁹	1997	41	36	2	–	–	–	–	–	0	–
Croes <i>et al.</i> ¹³⁰	1998	8	8	0	8	30	–	6	8	0	
Lezoche <i>et al.</i> ¹³¹	1998	1	0	0	1	–	3	–	–	0	
Meissner ¹³²	1998	1	1	0	1	41	4.5	1	1	0	
Ott and Hohenberger ¹³³	1998	23	23	0	–	–	–	–	4	0	
Katkhouda <i>et al.</i> ¹³⁴	1999	9	9	0	–	–	–	5	0	0	
Closset <i>et al.</i> ¹³⁵	2000	16	16	1	16	35	8.1	10	7	0	15
Herman <i>et al.</i> ¹³⁶	2000	10	10	0	10	29.2	–	9	0	0	
Ichikawa <i>et al.</i> ¹³⁷	2000	24	13	2	20	–	–	12	10	0	–
Mouiel <i>et al.</i> ¹³⁸	2000	1	1	0	–	–	–	–	0	0	
Ji <i>et al.</i> ¹³⁹	2000	4	4	0	1	37	–	0	–	0	
Aseni <i>et al.</i> ³⁹	2001	1	0	0	1	25	5.5	1	0	0	
Charny <i>et al.</i> ⁵⁴	2001	12	8	1	10	34	8.6	–	0	0	–
Heeringa and Sardi ¹⁴⁰	2001	1	1	0	1	27	5.5	1	1	0	
Hung <i>et al.</i> ¹⁴¹	2001	12	12	0	6	46.8	5.9	2	4	0	
Kammula <i>et al.</i> ¹⁴²	2001	8	8	0	–	–	–	–	–	–	
Mamada <i>et al.</i> ¹⁴³	2001	1	1	0	0	26	4.5	0	0	0	
Reddy <i>et al.</i> ¹⁴⁴	2001	25	25	1	25	33	5.9	21	3	0	25
Terkivatan <i>et al.</i> ³⁰	2001	33	19	0	29	36	–	27	12	0	
Wilkens <i>et al.</i> ¹⁴⁵	2001	10	10	0	8	38.9	7.4	–	–	0	
Antonetti <i>et al.</i> ¹⁴⁶	2002	1	1	0	–	–	–	–	–	0	
Farges <i>et al.</i> ¹⁴⁷	2002	2	2	0	–	–	–	–	–	0	
Marini <i>et al.</i> ¹⁴⁸	2002	7	7	1	7	37.4	13.5	0	7	3	–
Croce <i>et al.</i> ¹⁴⁹	2003	2	2	0	–	–	–	–	–	0	
Descottes <i>et al.</i> ¹⁵⁰	2003	17	17	0	–	–	–	–	0	0	
Ho <i>et al.</i> ¹⁵¹	2003	1	1	0	–	–	3.2	–	–	0	
Morino <i>et al.</i> ¹⁵²	2003	5	5	0	–	–	–	–	–	0	

Table 1 Continued

Study	Year	HCA (n)	Resected (n)	HCC (n)	Female (n)	Mean age (y)	Mean diameter (cm)	OC use (n)	Haemorrhage (n)	Embolization (n)	Smallest diameter (cm) ^a
Clarke <i>et al.</i> ¹⁵³	2004	8	8	0	–	–	–	–	–	0	
Kim <i>et al.</i> ¹⁵⁴	2004	11	11	2	–	–	–	–	0	0	–
Liu <i>et al.</i> ¹⁵⁵	2004	2	2	0	–	–	–	–	–	0	
Ronald <i>et al.</i> ¹⁵⁶	2004	3	3	0	0	36	8.3	0	0	0	
Atwell <i>et al.</i> ⁵⁷	2005	3	0	0	3	37	3.5	3	2	0	
Dulucq <i>et al.</i> ¹⁵⁷	2005	3	3	0	–	–	–	–	0	0	
Geller <i>et al.</i> ¹⁵⁸	2005	5	5	0	–	–	–	–	–	0	
Giusti <i>et al.</i> ¹⁵⁹	2005	1	1	0	0	45	18	0	0	0	
Psatha <i>et al.</i> ¹⁶⁰	2005	4	1	0	0	34.5	7	2	1	0	
Socas <i>et al.</i> ¹⁶¹	2005	2	0	0	0	29	–	2	1	0	
Toso <i>et al.</i> ¹⁶²	2005	23	23	2	–	–	–	–	10	2	6.4
Erdogan <i>et al.</i> ⁵⁸	2006	22	16	0	22	35.8	7.2	17	22	1	
Learn <i>et al.</i> ¹⁶³	2006	1	1	0	–	–	–	–	–	0	
Schemmer <i>et al.</i> ¹⁶⁴	2006	7	7	0	–	–	–	–	–	0	
Tang <i>et al.</i> ¹⁶⁵	2006	1	1	0	–	–	–	–	–	0	
Vibert <i>et al.</i> ¹⁶⁶	2006	3	3	0	–	–	–	–	–	0	
Van der Windt <i>et al.</i> ¹⁶⁷	2006	48	16	0	48	36	–	45	13	3	
Ardito <i>et al.</i> ¹⁶⁸	2007	7	7	0	–	–	–	–	0	0	
Chaib <i>et al.</i> ¹⁶⁹	2007	28	28	0	24	36.3	8.0	22	3	0	
Dagher <i>et al.</i> ¹⁷⁰	2007	6	6	0	–	–	–	–	–	0	
Hompes <i>et al.</i> ¹⁷¹	2007	2	2	0	–	–	–	–	–	0	
Ibrahim <i>et al.</i> ¹⁷²	2007	5	5	0	1	37.2	8.1	–	0	0	
Koffron <i>et al.</i> ¹⁷³	2007	47	47	0	–	–	–	–	–	0	
Nissen <i>et al.</i> ¹⁷⁴	2007	2	2	0	2	46.5	5.3	–	0	0	
Poultides <i>et al.</i> ¹⁷⁵	2007	1	1	0	1	33	7	–	0	0	
Reddy <i>et al.</i> ¹⁷⁶	2007	25 ^b	25	0	24	38	8.5	15	–	0	
Stoot <i>et al.</i> ³	2007	11	2	0	10	34	7	9	11	11	
Teeuwen <i>et al.</i> ¹⁷⁷	2007	2	2	0	2	29.5	–	2	0	0	
Balaa <i>et al.</i> ¹⁷⁸	2008	1	1	0	–	–	–	–	–	0	
Buell <i>et al.</i> ¹⁷⁹	2008	25	25	0	–	–	–	–	–	0	
Cho <i>et al.</i> ²⁸	2008	41	41	2	38	36	–	22	12	0	5.7
Feng <i>et al.</i> ¹⁸⁰	2008	17	17	0	–	–	–	–	–	0	
Machado <i>et al.</i> ¹⁸¹	2008	3	3	0	–	–	–	–	–	0	
Micchelli <i>et al.</i> ³¹	2008	17	17	3	–	–	–	^c	–	0	4
Petri <i>et al.</i> ¹⁸²	2008	22	22	0	20	38.3	7.7	–	–	0	
Popescu <i>et al.</i> ¹⁸³	2008	1	1	0	1	38	7.5	–	–	0	
Pulitano <i>et al.</i> ¹⁸⁴	2008	7	7	0	–	–	–	–	–	0	
Spencer <i>et al.</i> ¹⁸⁵	2008	1	1	0	–	–	–	–	–	0	
Troisi <i>et al.</i> ¹⁸⁶	2008	11	11	0	–	–	–	–	–	0	
Abu Hilal <i>et al.</i> ¹⁸⁷	2009	8	8	0	–	–	–	–	–	0	
Al Awad-Jibara <i>et al.</i> ¹⁸⁸	2009	1	1	0	1	40	5.8	0	0	0	
Bioulac-Sage <i>et al.</i> ¹⁶	2009	128	128	5	116	41	7	106	23	0	–
Bryant <i>et al.</i> ¹⁸⁹	2009	23	23	0	–	–	–	–	–	0	
Deneve <i>et al.</i> ¹⁵	2009	124	119	5	116	39	–	68	31	5	–
Dokmak <i>et al.</i> ¹⁴	2009	91	91	9	79	–	–	70	22	–	2–5
Ito <i>et al.</i> ¹⁹⁰	2009	5	5	0	–	–	–	–	–	0	
Machado <i>et al.</i> ¹⁹¹	2009	3	3	0	3	–	11.6	–	–	0	
Skalicky <i>et al.</i> ¹⁹²	2009	9	9	0	–	–	–	–	–	0	
Tomus <i>et al.</i> ¹⁹³	2009	3	3	0	–	–	–	–	–	0	
Watkins <i>et al.</i> ¹⁹⁴	2009	1	1	0	0	45	2.1	0	0	0	
Total		1617	1445	50	1075			787	400	35	

^aSmallest size of HCAs showing malignant transformation.^bThis study contained 2 groups, 25 patients without and 7 with glycogen storage disease (GSD) type Ia, of which the latter was excluded.^cAll cases with malignant transformation included OC use.

HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; OCs, oral contraceptives; –, no data available or not reported.

Table 2 Overview of reported single cases of malignant transformation of hepatocellular adenomas into hepatocellular carcinomas

Reference	Year	Age/ gender	Use and duration of OCs or steroids (years)	Number of HCAs and size at time of diagnosis of HCC	Time to HCA diagnosis (years) ^a	Interval between diagnosis of HCA and HCC (years)	Haemorrhage	Resected	Outcome
Tesluk and Lawrie ²⁶	1981	34/F	Yes, 5	Solitary, 16 cm	5	3	Yes	Yes	Postoperative death after one month
Gordon <i>et al.</i> ²²	1986	36/F	Yes, 14	Solitary, 13 cm	14	3	Yes	Yes	Disease free
Gyorffy <i>et al.</i> ²⁰	1989	53/F	Yes, 19	Multiple (3), 12 cm	19	2	No	No	Tumour-related death after 7 months
Korula <i>et al.</i> ¹⁹⁵	1991	40/F	Yes, 15	Solitary, 6.5 cm	21	None	No	Yes	Disease free
Ferrell ¹⁹⁶	1993	29/F	Yes, 0.5	Solitary, 18 cm	5	None	No	Yes	Disease free
Foster and Berman ¹⁹	1994	56/F	Yes, 10	Multiple (3–4)	10	5	No	No	Tumour-related death after 5 months
Herman <i>et al.</i> ¹⁹⁷	1994	30/F	Yes, 15	–	15	None	No	Yes	n/a
Herman <i>et al.</i> ¹⁹⁷	1994	37/F	Yes, 20	–	20	None	No	Yes	n/a
Perret <i>et al.</i> ¹⁹⁸	1996	24/F	Yes, 3	Solitary, 14 cm	3	None	No	Yes	Disease free
Scott <i>et al.</i> ¹⁹⁹	1996	22/M	No	Solitary, 6 cm	–	None	No	Yes	Disease free
Ye <i>et al.</i> ²¹	1999	42/F	Yes, 25	Multiple (2), 9 cm	25	None	Yes	Yes	Disease free
Larson <i>et al.</i> ²⁵	2002	52/M	No	Solitary, 12 cm	–	11	Yes	Yes	Recurrence after 6 years
Chuang <i>et al.</i> ¹⁷	2002	19/M	Yes, 15 ^c	–	15	None	No	Yes	n/a
Chuang <i>et al.</i> ¹⁷	2002	46/F	No	Solitary, 10 cm	–	None	No	Yes	n/a
Ito <i>et al.</i> ²³	2003	57/F	Yes, 1 month	Solitary, 10 cm	30	None	Yes	Yes	Disease free
Burri <i>et al.</i> ²⁰⁰	2006	40/F	Yes, 4.5	Solitary, 6 cm	16	None	No	Yes	Disease free
Colovic <i>et al.</i> ²⁷	2007	70/F	No	Solitary, 11.5 cm	–	None	No	Yes	Disease free
Gorayski <i>et al.</i> ¹⁸	2008	35/M	Yes, 2	Solitary, 9 cm	10	None	No	Yes	Disease free
Kim <i>et al.</i> ²⁴	2009	53/M	No	Solitary, 4.5 cm	–	None	Yes	Yes	Disease free

^aTime to HCA diagnosis since start of oral contraceptive therapy (which may have been discontinued before diagnosis).

^bThis case is also enlisted in Table 1.

^cOral prednisolone.

HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; OCs, oral contraceptives; –, no data available or not reported.

11.6 cm in largest diameter. No tumour smaller than 8 cm showed malignant transformation in this study. As shown in Table 2, the mean size of solitary HCAs with features of malignant alteration reported in the retrieved case reports was 10.5 cm (range 4.5 to 18 cm). Overall, the smallest size at which malignant transformation was reported in the literature was 4 cm. This malignant alteration occurred in a solitary tumour of a 23-year-old woman who had taken OCs for 8 years.³¹ In the series of 91 patients of Dokmak *et al.*,¹⁴ malignant alteration of either solitary or multifocal HCAs was seen in nine cases. In this study, only one case of malignant transformation was observed in an adenoma measuring less than 5 cm in diameter (2–5 cm, exact size not presented), concerning a male individual with a history of steroid intake. Overall, the current literature search showed that a total of three cases of malignant alteration (4.4% of all HCAs showing this phenomenon) occurred in a tumour measuring less than 5 cm in diameter.^{14,24,31}

Discussion

This systematic review has focussed on the risk of malignant transformation of HCAs into HCCs. The present study shows that malignant alteration is a rare complication of these uncommon benign tumours. By performing a systematic search of studies reporting cases of this benign liver disease over the past 40 years

and combining the data on these HCAs, a total of 1568 reported HCAs were found. The overall frequency of malignant transformation reported was 4.2% among all adenoma cases and 4.5% among all resected HCAs.

Although earlier series of HCAs had already shown one or two cases, Foster and Berman¹⁹ were the first to report an estimated risk of malignant transformation, as they found a frequency of 13%. Barthelmes and Tait,¹³ Cho *et al.*²⁸ and Micchelli *et al.*³¹ used a similar approach for determining the incidence of malignant degeneration employed in the current study. However, these three studies identified a remarkably smaller number of case series than included in the current review, and, moreover, the latter study did not include cases of HCAs in which no malignant alteration was found.³¹ Additionally, most case series used in the frequency estimation comprised a limited sample size and reported only on resected adenomas. This could have led to an overestimation of the true risk, apart from the selection bias of reported studies and cases in general. The series of Dokmak *et al.*,¹⁴ Deneve *et al.*¹⁵ and Bioulac-Sage *et al.*¹⁶ seem more robust for estimating the frequency of malignant alteration, as these authors analysed a larger population containing 91, 124 and 128 patients, respectively (cases with adenomatosis or GSD not included). Hepatic adenomatosis is regarded as a different entity by many authors concerning presentation and size and number of the adenomas, as well as the different therapeutic options.^{12,13} Equally, several

groups have recently reported germ line mutations of hepatocyte nuclear factor 1 α inactivation in adenomatosis, and this has been suggested to be associated with maturity-onset diabetes of the young type 3.^{32–34} Also, these mutations may have implications on the risk of malignant degeneration. Therefore, and also to limit heterogeneity, liver adenomatosis was excluded in the present review. As previously mentioned, patients with known GSDs are at a higher risk of developing HCAs^{11,35} and were therefore not included in the current review.

Risk factors of malignant transformation of hepatocellular adenomas

Although the risk of malignant transformation seems small (4.2%), this is a serious complication which cannot be neglected. As HCAs are difficult to discriminate from HCCs, because of similar imaging characteristics and histopathological features, it is important to identify factors that increase the risk of malignant transformation. Unfortunately, in the current study a true risk analysis based on tumour size was difficult to perform as many studies only reported the mean size of the adenomas included. However, as three cases have been reported in which malignant transformation occurred in a tumour measuring less than 5 cm in diameter, the recommendation to only treat HCAs larger than 5 cm in diameter in order to prevent malignant transformation is open for debate.^{14,24,31}

Upon reviewing the literature, several groups of patients were identified as having an increased risk of malignant alteration of these benign liver tumours. High-risk groups reported were those patients with a history of androgen or anabolic steroid intake,¹⁸ patients of male gender^{14,36} and, as previously stated, patients with GSD.^{11,37,38} Furthermore, as has been reported since the late 1970s, intake of OCs could potentially play a role in the enlargement of existing HCAs. To date, discontinuation of OC usage is still the advice given to patients that are diagnosed with an HCA,¹³ as several reports showed regression in size of the HCAs after cessation of OC intake.^{9,39,40} However, some case reports suggested that discontinuation of OCs will not abort the risk of malignant transformation.^{41,42} Therefore, even after discontinuation of OC use, long-term follow-up of patients with unresected HCAs remains necessary. Another proposed risk factor for malignant alteration is the presence of dysplasia in HCAs. This characteristic harbours a risk of progression to HCC.^{43–47}

Several studies have identified mutations of the β -catenin gene in HCAs and reported that activated β -catenin mutations deregulate the β -catenin pathway. This pathway is part of the more complex Wnt signalling pathway which plays a major role in the proliferation of liver cells.^{36,48–50} These mutations may thus lead to hyperproliferation of liver cells and, consequently, malignancy. The Bordeaux group has performed genotype–phenotype analyses in HCAs and identified four different tumour subtypes with specific characteristics: (i) hepatocyte nuclear factor 1 α (HNF1 α) mutated (30%–50%), (ii) β -catenin-activated (10–15%), (iii) inflammatory (35%) and (iv) unclassified tumours (5%–

Table 3 Types of HCAs and their immunohistochemical markers

HCA type	Frequency (%)	Malignant transformation	Markers
β -catenin activated	10–15	Yes	β -catenin+/GS+
HNF1 α inactivated	30–50	Rarely	LFABP–
Inflammatory	35	No	SAA+/CRP+
Unclassified	5–10	No	None

CRP, C-reactive protein; GS, glutamine synthetase; HCA, hepatocellular adenoma; HNF1 α , hepatocyte nuclear factor 1 α ; LFABP, liver-fatty acid binding protein; SAA, serum amyloid A; +, positive; –, negative.

10%).^{36,51,52} Hepatocellular carcinoma associated with adenoma was found in 46% of β -catenin-mutated tumours, whereas this has never been observed in inflammatory lesions and rarely found in HNF1 α -mutated tumours. This suggests that HCAs with β -catenin activation carry a higher risk of malignant transformation. Furthermore, the Bordeaux group identified four immunohistochemical markers that characterize each of the four HCA subtypes with high specificity and sensitivity: liver-fatty acid binding protein (L-FABP), glutamine synthetase (GS), nuclear β -catenin and serum amyloid A (SAA).⁵³ They found absence of L-FABP expression to indicate HNF1 α mutation, whereas combined GS overexpression and nuclear β -catenin staining suggested β -catenin-activating mutations. Finally, the Bordeaux group noted that SAA staining and overexpression of C-reactive protein (CRP) predicted inflammatory HCA. These markers have proven to be a promising method to identify adenoma patients at risk of developing HCC. Table 3 provides an overview of HCA subtypes and their immunohistochemical markers.

Future treatment perspectives

As for future treatment perspectives, more research is needed to investigate the mechanism of malignant degeneration. Only then can this group of predominantly young patients be withheld a potentially unnecessary liver resection, while this surgical treatment has still a reported morbidity and mortality of up to 27% and 3%, respectively.^{30,54–56} At present, for all patients presenting with one or more HCAs larger than 5 cm, resection is the treatment option of choice in accordance with the current guidelines. Only 4.2% of HCAs will have actual foci of HCC, and therefore a considerable number of resections will be performed in vain. However, this rate should preferably be seen as an upper limit of the true frequency as publication bias might have occurred. After all, men who have an anabolic steroid-induced adenoma containing foci of malignancy are more likely to be reported in the literature than those adenoma patients without malignant transformation. Nevertheless, over 95% of all patients presenting with HCAs measuring over 5 cm, will unnecessarily be exposed to a potentially hazardous surgical procedure. By identifying those patients who will derive most benefit from surgery as their HCA harbours an increased risk for malignant alteration, fewer patients will have to undergo this unnecessary surgery. The Bordeaux HCA markers are

a promising risk prediction tool. However, biopsy could lead to haemorrhage, sample errors or tumour seeding, but these potential complications are rare in experienced centres. Also, the value of β -catenin staining needs to be studied more intensively. Recently, interest has turned towards less invasive procedures to treat patients that present with HCAs larger than 5 cm. There is preliminary evidence to suggest that developments in minimally invasive techniques such as (percutaneous) radiofrequency ablation (RFA) or microwave ablation may alter the treatment of HCA. The limited data so far available suggest that these techniques can be performed with low morbidity and zero mortality, but additional research is required to explore their exact role in adenoma treatment.⁵⁷

Recently, two groups have reported the therapeutic effects of selective arterial embolization to stop haemorrhaging from ruptured adenomas.^{3,58} They also showed that embolizing ruptured adenomas prevented growth of these lesions. Subsequently, selective arterial embolization was utilized in a number of non-haemorrhaging adenomas.³ During follow-up, none of these adenomas grew and the majority even regressed in size. On examining the haemorrhaging and non-haemorrhaging adenomas separately, a statistically significant decrease in size was noted in both groups. It is this tumour regression, and its probable subsequent reduction of the risk of severe haemorrhaging and malignant transformation, that might propose selective arterial embolization as a novel treatment for large unruptured HCAs. As no significant complications from this treatment were reported arterial embolization of HCAs might be the direction for further future research.^{3,58} To the best of our knowledge, no studies have been performed to specifically investigate this treatment.

In conclusion, the current review shows that malignant transformation of HCAs into HCCs is a rare complication of these uncommon benign tumours. By pooling data of series and case reports, comprising more than 1600 reported HCAs, we found an overall frequency of malignant transformation of 4.2% for all adenomas and of 4.5% for all resected adenomas. A multicentre study with a large registry of HCAs is paramount for estimating the actual risk of malignant transformation. Further research should focus on the underlying mechanisms of malignant transformation of HCAs into HCCs, associated risk factors and the use of new tumour markers. By means of a better selection of precisely which patients with an HCA present with an increased risk of malignant degeneration – and who could therefore derive the greatest benefit from treatment – a reduction in unnecessary liver resections can be achieved. This would reduce the risks associated with surgery in these predominantly young patients.

Conflicts of interest

None declared.

References

1. Rooks JB, Ory HW, Ishak KG, Strauss LT, Greenspan JR, Hill AP *et al.* (1979) Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. *JAMA* 242:644–648.
2. Leese T, Farges O, Bismuth H. (1988) Liver cell adenomas. A 12-year surgical experience from a specialist hepato-biliary unit. *Ann Surg* 208:558–564.
3. Stoot JH, van der Linden E, Terpstra OT, Schaapherder AF. (2007) Life-saving therapy for haemorrhaging liver adenomas using selective arterial embolization. *Br J Surg* 94:1249–1253.
4. Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Tilanus HW, JN IJ. (2001) Treatment of ruptured hepatocellular adenoma. *Br J Surg* 88:207–209.
5. Edmondson HA, Henderson B, Benton B. (1976) Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med* 294:470–472.
6. Soe KL, Soe M, Gluud C. (1992) Liver pathology associated with the use of anabolic-androgenic steroids. *Liver* 12:73–79.
7. Wanless IR, Medline A. (1982) Role of estrogens as promoters of hepatic neoplasia. *Lab Invest* 46:313–320.
8. Reddy KR, Schiff ER. (1993) Approach to a liver mass. *Semin Liver Dis* 13:423–435.
9. Buhler H, Pirovino M, Akobiantz A, Altorf J, Weitzel M, Maranta E *et al.* (1982) Regression of liver cell adenoma. A follow-up study of three consecutive patients after discontinuation of oral contraceptive use. *Gastroenterology* 82:775–782.
10. Edmondson HA, Reynolds TB, Henderson B, Benton B. (1977) Regression of liver cell adenomas associated with oral contraceptives. *Ann Intern Med* 86:180–182.
11. Labrune P, Trioche P, Duvaltier I, Chevalier P, Odievre M. (1997) Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *J Pediatr Gastroenterol Nutr* 24:276–279.
12. Flejou JF, Barge J, Menu Y, Degott C, Bismuth H, Potet F *et al.* (1985) Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology* 89:1132–1138.
13. Barthelmes L, Tait IS. (2005) Liver cell adenoma and liver cell adenomatosis. *HPB (Oxford)* 7:186–196.
14. Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D *et al.* (2009) A Single Center Surgical Experience of 122 Patients with Single and Multiple Hepatocellular Adenomas. *Gastroenterology* 137:1698–1705.
15. Deneve JL, Pawlik TM, Cunningham S, Clary B, Reddy S, Scoggins CR *et al.* (2009) Liver cell adenoma: a multicenter analysis of risk factors for rupture and malignancy. *Ann Surg Oncol* 16:640–648.
16. Bioulac-Sage P, Laumonier H, Couchy G, Le Bail B, Sa Cunha A, Rullier A *et al.* (2009) Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. *Hepatology* 50:481–489.
17. Chuang WY, Chen TC, Hsu HL, Lee WC, Jeng LB, Huang SF. (2002) Liver cell adenoma with concomitant hepatocellular carcinoma: report of two cases. *J Formos Med Assoc* 101:798–802.
18. Gorayski P, Thompson CH, Subhash HS, Thomas AC. (2008) Hepatocellular carcinoma associated with recreational anabolic steroid use. *Br J Sports Med* 42:74–75. discussion 5.
19. Foster JH, Berman MM. (1994) The malignant transformation of liver cell adenomas. *Arch Surg* 129:712–717.
20. Gyorffy EJ, Bredfeldt JE, Black WC. (1989) Transformation of hepatic cell adenoma to hepatocellular carcinoma due to oral contraceptive use. *Ann Intern Med* 110:489–490.
21. Ye MQ, Suriawinata A, Ben Haim M, Parsons R, Schwartz ME. (1999) A 42-year-old woman with liver masses and long-term use of oral contraceptives. *Semin Liver Dis* 19:339–344.

22. Gordon SC, Reddy KR, Livingstone AS, Jeffers LJ, Schiff ER. (1986) Resolution of a contraceptive-steroid-induced hepatic adenoma with subsequent evolution into hepatocellular carcinoma. *Ann Intern Med* 105:547–549.
23. Ito M, Sasaki M, Wen CY, Nakashima M, Ueki T, Ishibashi H *et al.* (2003) Liver cell adenoma with malignant transformation: a case report. *World J Gastroenterol* 9:2379–2381.
24. Kim DH, Kim SU, Nam DH, Choi YJ, Park SM, Lee CK *et al.* (2009) A case of hepatocellular carcinoma within hepatocellular adenoma in a non-cirrhotic male. *Korean J Intern Med* 24:147–152.
25. Larson KA, Weber SM, Fong Y, Blumgart LH. (2002) Malignant transformation of hepatic adenoma with recurrence after resection. *HPB (Oxford)* 4:139–143.
26. Tesluk H, Lawrie J. (1981) Hepatocellular adenoma. Its transformation to carcinoma in a user of oral contraceptives. *Arch Pathol Lab Med* 105:296–299.
27. Colovic R, Grubor N, Micev M, Radak V. (2007) Hepatocellular adenoma with malignant alteration. *Hepatogastroenterology* 54:386–388.
28. Cho SW, Marsh JW, Steel J, Holloway SE, Heckman JT, Ochoa ER *et al.* (2008) Surgical management of hepatocellular adenoma: take it or leave it? *Ann Surg Oncol* 15:2795–2803.
29. Ault GT, Wren SM, Ralls PW, Reynolds TB, Stain SC. (1996) Selective management of hepatic adenomas. *Am Surg* 62:825–829.
30. Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW *et al.* (2001) Indications and long-term outcome of treatment for benign hepatic tumors: a critical appraisal. *Arch Surg* 136:1033–1038.
31. Micchelli ST, Vivekanandan P, Boitnott JK, Pawlik TM, Choti MA, Torbenson M. (2008) Malignant transformation of hepatic adenomas. *Mod Pathol* 21:491–497.
32. Montano-Loza A, Rios-Vaca A, Remes-Troche JM, Meza-Junco J, Trinidad-Hernandez S. (2002) Hepatic adenomatosis in an Hispanic patient. A case report and review of the literature. *Ann Hepatol* 1:136–139.
33. Bacq Y, Jacquemin E, Balabaud C, Jeannot E, Scotto B, Branchereau S *et al.* (2003) Familial liver adenomatosis associated with hepatocyte nuclear factor 1alpha inactivation. *Gastroenterology* 125:1470–1475.
34. Greaves WO, Bhattacharya B. (2008) Hepatic adenomatosis. *Arch Pathol Lab Med* 132:1951–1955.
35. Bioulac-Sage P, Laumonier H, Laurent C, Zucman-Rossi J, Balabaud C. (2008) Hepatocellular adenoma: what is new in 2008. *Hepatol Int* 2:316–321.
36. Zucman-Rossi J, Jeannot E, Nhieu JT, Scoazec JY, Guettier C, Rebouissou S *et al.* (2006) Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. *Hepatology* 43:515–524.
37. Franco LM, Krishnamurthy V, Bali D, Weinstein DA, Arn P, Clary B *et al.* (2005) Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. *J Inherit Metab Dis* 28:153–162.
38. Velazquez I, Alter BP. (2004) Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 77:257–267.
39. Aseni P, Sansalone CV, Sammartino C, Benedetto FD, Carrafiello G, Giacomoni A *et al.* (2001) Rapid disappearance of hepatic adenoma after contraceptive withdrawal. *J Clin Gastroenterol* 33:234–236.
40. Kawakatsu M, Vilgrain V, Erlinger S, Nahum H. (1997) Disappearance of liver cell adenoma: CT and MR imaging. *Abdom Imaging* 22:274–276.
41. Mariani AF, Livingstone AS, Pereiras RV, Jr, van Zuiden PE, Schiff ER. (1979) Progressive enlargement of an hepatic cell adenoma. *Gastroenterology* 77:1319–1325.
42. Marks WH, Thompson N, Appleman H. (1988) Failure of hepatic adenomas (HCA) to regress after discontinuance of oral contraceptives. An association with focal nodular hyperplasia (FNH) and uterine leiomyoma. *Ann Surg* 208:190–195.
43. Anthony PP, Vogel CL, Barker LF. (1973) Liver cell dysplasia: a premalignant condition. *J Clin Pathol* 26:217–223.
44. Ho JC, Wu PC, Mak TK. (1981) Liver cell dysplasia in association with hepatocellular carcinoma, cirrhosis and hepatitis B surface antigen in Hong Kong. *Int J Cancer* 28:571–574.
45. Lee RG, Tsamandas AC, Demetris AJ. (1997) Large cell change (liver cell dysplasia) and hepatocellular carcinoma in cirrhosis: matched case-control study, pathological analysis, and pathogenetic hypothesis. *Hepatology* 26:1415–1422.
46. Su Q, Benner A, Hofmann WJ, Otto G, Pichlmayr R, Bannasch P. (1997) Human hepatic preneoplasia: phenotypes and proliferation kinetics of foci and nodules of altered hepatocytes and their relationship to liver cell dysplasia. *Virchows Arch* 431:391–406.
47. Tao LC. (1991) Oral contraceptive-associated liver cell adenoma and hepatocellular carcinoma. Cytomorphology and mechanism of malignant transformation. *Cancer* 68:341–347.
48. Chen YW, Jeng YM, Yeh SH, Chen PJ. (2002) P53 gene and Wnt signaling in benign neoplasms: beta-catenin mutations in hepatic adenoma but not in focal nodular hyperplasia. *Hepatology* 36:927–935.
49. Nelson WJ, Nusse R. (2004) Convergence of Wnt, beta-catenin, and cadherin pathways. *Science* 303:1483–1487.
50. Thompson MD, Monga SP. (2007) WNT/beta-catenin signaling in liver health and disease. *Hepatology* 45:1298–1305.
51. Bioulac-Sage P, Blanc JF, Rebouissou S, Balabaud C, Zucman-Rossi J. (2007) Genotype phenotype classification of hepatocellular adenoma. *World J Gastroenterol* 13:2649–2654.
52. Bluteau O, Jeannot E, Bioulac-Sage P, Marques JM, Blanc JF, Bui H *et al.* (2002) Bi-allelic inactivation of TCF1 in hepatic adenomas. *Nat Genet* 32:312–315.
53. Bioulac-Sage P, Rebouissou S, Thomas C, Blanc JF, Saric J, Sa Cunha A *et al.* (2007) Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. *Hepatology* 46:740–748.
54. Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y *et al.* (2001) Management of 155 patients with benign liver tumours. *Br J Surg* 88:808–813.
55. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al.* (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 236:397–406. discussion -7.
56. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK *et al.* (2004) Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 240:698–708. discussion -10.
57. Atwell TD, Brandhagen DJ, Charboneau JW, Nagorney DM, Callstrom MR, Farrell MA. (2005) Successful treatment of hepatocellular adenoma with percutaneous radiofrequency ablation. *AJR Am J Roentgenol* 184:828–831.
58. Erdogan D, Busch OR, van Delden OM, Ten Kate FJ, Gouma DJ,

- van Gulik TM. (2006) Management of spontaneous haemorrhage and rupture of hepatocellular adenomas. A single centre experience. *Liver Int* 26:433–438.
59. Malt RA, Hershberg RA, Miller WL. (1970) Experience with benign tumors of the liver. *Surg Gynecol Obstet* 130:285–291.
 60. Kay S, Schatzki PF. (1971) Ultrastructure of a benign liver cell adenoma. *Cancer* 28:755–762.
 61. Horvath E, Kovacs K, Ross RC. (1972) Ultrastructural findings in a well-differentiated hepatoma. *Digestion* 7:74–82.
 62. Motsay GJ, Gamble WG. (1972) Clinical experience with hepatic adenomas. *Surg Gynecol Obstet* 134:415–418.
 63. Baum JK, Bookstein JJ, Holtz F, Klein EW. (1973) Possible association between benign hepatomas and oral contraceptives. *Lancet* 2:926–929.
 64. Contostavlos DL. (1973) Letter: benign hepatomas and oral contraceptives. *Lancet* 2:1200.
 65. Davis JB, Schrenken JR, Zimmerman O. (1973) Massive hemoperitoneum from rupture of benign hepatocellular adenoma. *Surgery* 73:181–184.
 66. Hermann RE, David TE. (1973) Spontaneous rupture of the liver caused by hepatomas. *Surgery* 74:715–719.
 67. Albritton DR, Tompkins RK, Longmire WP, Jr. (1974) Hepatic cell adenoma: a report of four cases. *Ann Surg* 180:14–19.
 68. Berg JW, Ketalaar RJ, Rose EF, Vernon RG. (1974) Letter: hepatomas and oral contraceptives. *Lancet* 2:349–350.
 69. Kelso DR. (1974) Letter: benign hepatomas and oral contraceptives. *Lancet* 1:315–316.
 70. Knapp WA, Ruebner BH. (1974) Letter: hepatomas and oral contraceptives. *Lancet* 1:270–271.
 71. Tountas C, Paraskevas G, Deligeorgi H. (1974) Letter: benign hepatoma and oral contraceptives. *Lancet* 1:1351–1352.
 72. Ameriks JA, Thompson NW, Frey CF, Appelman HD, Walter JF. (1975) Hepatic cell adenomas, spontaneous liver rupture, and oral contraceptives. *Arch Surg* 110:548–557.
 73. Antoniadis K, Campbell WN, Hecksher RH, Kessler WB, McCarthy GE, Jr. (1975) Liver cell adenoma and oral contraceptives. Double tumor development. *JAMA* 234:628–629.
 74. Antoniadis K, Brooks CE, Jr. (1975) Hemoperitoneum from liver cell adenoma in a patient on oral contraceptives. *Surgery* 77:137–139.
 75. Galloway SJ, Casarella WJ, Lattes R, Seamam WB. (1975) Minimal deviation hepatoma. A new entity. *Am J Roentgenol Radium Ther Nucl Med* 125:184–192.
 76. Mdel DG, Fox JA, Jones RW. (1975) Letter: multiple hepatic adenomas associated with an oral contraceptive. *Lancet* 1:865.
 77. Nissen ED, Kent DR. (1975) Liver tumors and oral contraceptives. *Obstet Gynecol* 46:460–467.
 78. Stenwig AE, Solgaard T. (1975) Ruptured benign hepatoma associated with an oral contraceptive. A case report. *Virchows Arch A Pathol Anat Histol* 367:337–343.
 79. Ammentorp PA, Carson RP. (1976) Hepatocellular adenoma and oral contraceptives. *Ohio State Med J* 72:283–286.
 80. Andersen PH, Packer JT. (1976) Hepatic adenoma. Observations after estrogen withdrawal. *Arch Surg* 111:898–900.
 81. Baek S, Sloane CE, Futterman SC. (1976) Benign liver cell adenoma associated with use of oral contraceptive agents. *Ann Surg* 183:239–242.
 82. Brander WL, Vosnides G, Ogg CS, West IE. (1976) Multiple hepatocellular tumours in a patient treated with oral contraceptives. *Virchows Arch A Pathol Anat Histol* 370:69–76.
 83. Lansing PB, McQuitty JT, Bradburn DM. (1976) Benign liver tumors: what is their relationship to oral contraceptives? *Am Surg* 42:744–760.
 84. Sears HF, Smith G, Powell RD. (1976) Hepatic adenoma associated with oral contraceptive use: an unusual clinical presentation. *Arch Surg* 111:1399–1403.
 85. Chan CK, Detmer DE. (1977) Proper management of hepatic adenoma associated with oral contraceptives. *Surg Gynecol Obstet* 144:703–706.
 86. Fechner RE. (1977) Benign hepatic lesions and orally administered contraceptives. A report of seven cases and a critical analysis of the literature. *Hum Pathol* 8:255–268.
 87. Fortner JG, Kim DK, Maclean BJ, Barrett MK, Iwatsuki S, Turnbull AD et al. (1978) Major hepatic resection for neoplasia: personal experience in 108 patients. *Ann Surg* 188:363–371.
 88. Gold JH, Guzman IJ, Rosai J. (1978) Benign tumors of the liver. Pathologic examination of 45 cases. *Am J Clin Pathol* 70:6–17.
 89. Ramseur WL, Cooper MR. (1978) Asymptomatic liver cell adenomas. Another case of resolution after discontinuation of oral contraceptive use. *JAMA* 239:1647–1648.
 90. Bird D, Vowles K, Anthony PP. (1979) Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy. *Br J Surg* 66:212–213.
 91. Cady B, Bonneval M, Fender HR, Jr. (1979) Elective hepatic resection. *Am J Surg* 137:514–521.
 92. Catalano PW, Martin EW, Jr, Ellison C, Carey LC. (1979) Reasonable surgical treatment for tumors of the liver associated with the use of oral contraceptives. *Surg Gynecol Obstet* 148:759–763.
 93. Wheeler PG, Melia W, Dubbins P, Jones B, Nunnerley H, Johnson P et al. (1979) Non-operative arterial embolisation in primary liver tumours. *Br Med J* 2:242–244.
 94. Weil R, 3rd, Koep LJ, Starzl TE. (1979) Liver resection for hepatic adenoma. *Arch Surg* 114:178–180.
 95. Kelly TR. (1980) Benign liver tumors: presenting profiles and treatment. *Am Surg* 46:398–402.
 96. Neuberger J, Portmann B, Nunnerley HB, Laws JW, Davis M, Williams R. (1980) Oral-contraceptive-associated liver tumours: occurrence of malignancy and difficulties in diagnosis. *Lancet* 1:273–276.
 97. Herczeg B, Magyar E, Petroczy G, Kovacs I, Ling L, Csitary F. (1981) [Oral contraceptives and liver tumors]. *Orv Hetil* 122:1879–1883.
 98. Isman H, Bourgeon R, Rampal P, Koch G, Mattei S. (1981) [Benign solid hepatic tumors: report on six cases. Diagnostic and therapeutic problems (author's transl)]. *Chirurgie* 107:44–52.
 99. Thompson JF, Little JM. (1981) Liver resection for neoplasm. *Aust N Z J Surg* 51:274–279.
 100. Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF, 2nd. (1983) Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. *Gastroenterology* 84:994–1002.
 101. Meensook C, Sirisabya N. (1983) Benign hepatic tumor and oral contraceptives. *J Med Assoc Thai* 66:299–302.
 102. Thompson HH, Tompkins RK, Longmire WP, Jr. (1983) Major hepatic resection. A 25-year experience. *Ann Surg* 197:375–388.
 103. Cassinelli GB. (1985) [Hepatic adenoma and oral contraceptives: personal case]. *Ann Ital Chir* 57:101–107.
 104. Gonzalez F, Marks C. (1985) Hepatic tumors and oral contraceptives: surgical management. *J Surg Oncol* 29:193–197.

105. Welch TJ, Sheedy PF, 2nd, Johnson CM, Stephens DH, Charboneau JW, Brown ML *et al.* (1985) Focal nodular hyperplasia and hepatic adenoma: comparison of angiography, CT, US, and scintigraphy. *Radiology* 156:593–595.
106. Mathieu D, Bruneton JN, Drouillard J, Pointreau CC, Vasile N. (1986) Hepatic adenomas and focal nodular hyperplasia: dynamic CT study. *Radiology* 160:53–58.
107. Creagh TM, Rubin A, Evans DJ. (1988) Hepatic tumours induced by anabolic steroids in an athlete. *J Clin Pathol* 41:441–443.
108. Ringe B, Mauz S, Barg-Hock H, Kotzerke J, Pichlmayr R. (1989) [Surgery of benign liver tumors]. *Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir*:287–291.
109. Flowers BF, McBurney RP, Vera SR. (1990) Ruptured hepatic adenoma. A spectrum of presentation and treatment. *Am Surg* 56:380–383.
110. Iwatsuki S, Todo S, Starzl TE. (1990) Excisional therapy for benign hepatic lesions. *Surg Gynecol Obstet* 171:240–246.
111. Leborgne J, Lehur PA, Horeau JM, Dupas B, Bourcheix LM, Petiot JM *et al.* (1990) [Therapeutic problems caused by rupture of large hepatic adenoma with central location. Apropos of 3 cases]. *Chirurgie* 116:454–460.
112. Belghiti J, Pateron D, Panis Y, Vilgrain V, Flejou JF, Benhamou JP *et al.* (1993) Resection of presumed benign liver tumours. *Br J Surg* 80:380–383.
113. Arrive L, Flejou JF, Vilgrain V, Belghiti J, Najmark D, Zins M *et al.* (1994) Hepatic adenoma: MR findings in 51 pathologically proved lesions. *Radiology* 193:507–512.
114. Eckhauser FE, Knol JA, Raper SE, Thompson NW. (1994) Enucleation combined with hepatic vascular exclusion is a safe and effective alternative to hepatic resection for liver cell adenoma. *Am Surg* 60:466–471. discussion 72.
115. Golli M, Van Nhieu JT, Mathieu D, Zafrani ES, Cherqui D, Dhumeaux D *et al.* (1994) Hepatocellular adenoma: color Doppler US and pathologic correlations. *Radiology* 190:741–744.
116. Paineau J, Hamy A, Visset J. (1994) [Our surgical experience in the resection of benign hepatic tumors. Apropos of 31 cases]. *J Chir (Paris)* 131:461–465.
117. Paulson EK, McClellan JS, Washington K, Spritzer CE, Meyers WC, Baker ME. (1994) Hepatic adenoma: MR characteristics and correlation with pathologic findings. *AJR Am J Roentgenol* 163:113–116.
118. Pertschy J, Ruckert JC, Manger T. (1994) [Diagnosis and surgical therapy of benign liver tumors]. *Zentralbl Chir* 119:495–500.
119. Cherqui D, Rahmouni A, Charlotte F, Boulahdour H, Metreau JM, Meignan M *et al.* (1995) Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. *Hepatology* 22:1674–1681.
120. Cuesta MA, Meijer S, Paul MA, de Brauw LM. (1995) Limited laparoscopic liver resection of benign tumors guided by laparoscopic ultrasonography: report of two cases. *Surg Laparosc Endosc* 5:396–401.
121. Ferzli G, David A, Kiel T. (1995) Laparoscopic resection of a large hepatic tumor. *Surg Endosc* 9:733–735.
122. Nagorney DM. (1995) Benign hepatic tumors: focal nodular hyperplasia and hepatocellular adenoma. *World J Surg* 19:13–18.
123. Azagra JS, Goergen M, Gilbert E, Jacobs D. (1996) Laparoscopic anatomical (hepatic) left lateral segmentectomy-technical aspects. *Surg Endosc* 10:758–761.
124. Cheng PN, Shin JS, Lin XZ. (1996) Hepatic adenoma: an observation from asymptomatic stage to rupture. *Hepatogastroenterology* 43:245–248.
125. Kelly D, Emre S, Guy SR, Sheiner PA, Miller CM, Schwartz ME. (1996) Resection of benign hepatic lesions with selective use of total vascular isolation. *J Am Coll Surg* 183:113–116.
126. Vogl TJ, Hammerstingl R, Schwarz W, Mack MG, Muller PK, Pegios W *et al.* (1996) Superparamagnetic iron oxide – enhanced versus gadolinium-enhanced MR imaging for differential diagnosis of focal liver lesions. *Radiology* 198:881–887.
127. De Carlis L, Pirotta V, Rondinara GF, Sansalone CV, Colella G, Maione G *et al.* (1997) Hepatic adenoma and focal nodular hyperplasia: diagnosis and criteria for treatment. *Liver Transpl Surg* 3:160–165.
128. Krug B, Zieren HU, Jung G, Hemme A, Heindel W, Krings F. (1997) Late results after resection of benign hepatic tumors: clinical and radiological findings. *Eur Radiol* 7:327–332.
129. Weimann A, Ringe B, Klempnauer J, Lamesch P, Gratz KF, Prokop M *et al.* (1997) Benign liver tumors: differential diagnosis and indications for surgery. *World J Surg* 21:983–990. discussion 90–1.
130. Croes EA, van Gulik TM, Bosma A, de Wit LT, Gouma DJ. (1998) [Treatment of 8 patients with an acute hemorrhage in a hepatocellular adenoma at the Academic Medical Center, Amsterdam]. *Ned Tijdschr Geneeskde* 142:2463–2468.
131. Lezocoe E, Paganini AM, Feliciotti F, Guerrieri M, Lugnani F, Tamburini A. (1998) Ultrasound-guided laparoscopic cryoablation of hepatic tumors: preliminary report. *World J Surg* 22:829–835. discussion 35–36.
132. Meissner K. (1998) Hemorrhage caused by ruptured liver cell adenoma following long-term oral contraceptives: a case report. *Hepatogastroenterology* 45:224–225.
133. Ott R, Hohenberger W. (1998) [Focal nodular hyperplasia and liver cell adenoma: operation or observation?]. *Zentralbl Chir* 123:145–153.
134. Katkhouda N, Hurwitz M, Gugenheim J, Mavor E, Mason RJ, Waldrep DJ *et al.* (1999) Laparoscopic management of benign solid and cystic lesions of the liver. *Ann Surg* 229:460–466.
135. Closset J, Veys I, Peny MO, Braude P, Van Gansbeke D, Lambilliotte JP *et al.* (2000) Retrospective analysis of 29 patients surgically treated for hepatocellular adenoma or focal nodular hyperplasia. *Hepatogastroenterology* 47:1382–1384.
136. Herman P, Pugliese V, Machado MA, Montagnini AL, Salem MZ, Bacchella T *et al.* (2000) Hepatic adenoma and focal nodular hyperplasia: differential diagnosis and treatment. *World J Surg* 24:372–376.
137. Ichikawa T, Federle MP, Grazioli L, Nalesnik M. (2000) Hepatocellular adenoma: multiphasic CT and histopathologic findings in 25 patients. *Radiology* 214:861–868.
138. Mouiel J, Katkhouda N, Gugenheim J, Fabiani P. (2000) Possibilities of laparoscopic liver resection. *J Hepatobiliary Pancreat Surg* 7: 1–8.
139. Ji Y, Zhu X, Sun H, Tan Y, Ma Z, Ye Q *et al.* (2000) Hepatocellular adenoma and focal nodular hyperplasia: a series of 24 patients with clinicopathological and radiological correlation. *Chin Med J (Engl)* 113:852–857.
140. Heeringa B, Sardi A. (2001) Bleeding hepatic adenoma: expectant treatment to limit the extent of liver resection. *Am Surg* 67:927–929.
141. Hung CH, Changchien CS, Lu SN, Eng HL, Wang JH, Lee CM *et al.* (2001) Sonographic features of hepatic adenomas with pathologic correlation. *Abdom Imaging* 26:500–506.
142. Kammula US, Buell JF, Labow DM, Rosen S, Millis JM, Posner MC.

- (2001) Surgical management of benign tumors of the liver. *Int J Gastrointest Cancer* 30:141–146.
143. Mamada Y, Onda M, Tajiri T, Akimaru K, Yoshida H, Taniai N *et al.* (2001) Liver cell adenoma in a 26-year-old man. *J Nippon Med Sch* 68:516–519.
 144. Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D *et al.* (2001) Benign and solid tumors of the liver: relationship to sex, age, size of tumors, and outcome. *Am Surg* 67:173–178.
 145. Wilkens L, Bredt M, Flemming P, Becker T, Klempnauer J, Kreipe HH. (2001) Differentiation of liver cell adenomas from well-differentiated hepatocellular carcinomas by comparative genomic hybridization. *J Pathol* 193:476–482.
 146. Antonetti MC, Killelea B, Orlando R, 3rd. (2002) Hand-assisted laparoscopic liver surgery. *Arch Surg* 137:407–411. discussion 12.
 147. Farges O, Jagot P, Kirstetter P, Marty J, Belghiti J. (2002) Prospective assessment of the safety and benefit of laparoscopic liver resections. *J Hepatobiliary Pancreat Surg* 9:242–248.
 148. Marini P, Vilgrain V, Belghiti J. (2002) Management of spontaneous rupture of liver tumours. *Dig Surg* 19:109–113.
 149. Croce E, Olmi S, Bertolini A, Erba L, Magnone S. (2003) Laparoscopic liver resection with radiofrequency. *Hepatogastroenterology* 50:2088–2092.
 150. Descottes B, Glineur D, Lachachi F, Valleix D, Paineau J, Hamy A *et al.* (2003) Laparoscopic liver resection of benign liver tumors. *Surg Endosc* 17:23–30.
 151. Ho CL, Yu SC, Yeung DW. (2003) 11C-acetate PET imaging in hepatocellular carcinoma and other liver masses. *J Nucl Med* 44:213–221.
 152. Morino M, Morra I, Rosso E, Miglietta C, Garrone C. (2003) Laparoscopic vs open hepatic resection: a comparative study. *Surg Endosc* 17:1914–1918.
 153. Clarke D, Currie E, Madhavan K, Parks R, Garden O. (2004) Hepatic resection for benign non-cystic liver lesions. *HPB (Oxford)* 6:115–119.
 154. Kim J, Ahmad SA, Lowy AM, Buell JF, Pennington LJ, Moulton JS *et al.* (2004) An algorithm for the accurate identification of benign liver lesions. *Am J Surg* 187:274–279.
 155. Liu CL, Fan ST, Lo CM, Chan SC, Tso WK, Ng IO *et al.* (2004) Hepatic resection for incidentaloma. *J Gastrointest Surg* 8:785–793.
 156. Ronald M, Woodfield J, McCall J, Koea J. (2004) Hepatic adenomas in male patients. *HPB (Oxford)* 6:25–27.
 157. Dulucq JL, Wintringer P, Stabilini C, Berticelli J, Mahajna A. (2005) Laparoscopic liver resections: a single center experience. *Surg Endosc* 19:886–891.
 158. Geller DA, Tsung A, Maheshwari V, Rutstein LA, Fung JJ, Wallis Marsh J. (2005) Hepatic resection in 170 patients using saline-cooled radiofrequency coagulation. *HPB (Oxford)* 7:208–213.
 159. Giusti S, Donati F, Paolicchi A, Bartolozzi C. (2005) Hepatocellular adenoma: imaging findings and pathological correlation. *Dig Liver Dis* 37:200–205.
 160. Psatha EA, Semelka RC, Armao D, Woosley JT, Firat Z, Schneider G. (2005) Hepatocellular adenomas in men: MRI findings in four patients. *J Magn Reson Imaging* 22:258–264.
 161. Socas L, Zumbado M, Perez-Luzardo O, Ramos A, Perez C, Hernandez JR *et al.* (2005) Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. *Br J Sports Med* 39:e27.
 162. Toso C, Majno P, Andres A, Rubbia-Brandt L, Berney T, Buhler L *et al.* (2005) Management of hepatocellular adenoma: solitary-uncomplicated, multiple and ruptured tumors. *World J Gastroenterol* 11:5691–5695.
 163. Learn PA, Bowers SP, Watkins KT. (2006) Laparoscopic hepatic resection using saline-enhanced electrocautery permits short hospital stays. *J Gastrointest Surg* 10:422–427.
 164. Schemmer P, Friess H, Hinz U, Mehrabi A, Kraus TW, Z'Graggen K *et al.* (2006) Stapler hepatectomy is a safe dissection technique: analysis of 300 patients. *World J Surg* 30:419–430.
 165. Tang CN, Tsui KK, Ha JP, Yang GP, Li MK. (2006) A single-centre experience of 40 laparoscopic liver resections. *Hong Kong Med J* 12:419–425.
 166. Vibert E, Perniceni T, Levard H, Denet C, Shahri NK, Gayet B. (2006) Laparoscopic liver resection. *Br J Surg* 93:67–72.
 167. van der Windt DJ, Kok NF, Hussain SM, Zondervan PE, Alwayn IP, de Man RA *et al.* (2006) Case-orientated approach to the management of hepatocellular adenoma. *Br J Surg* 93:1495–1502.
 168. Ardito F, Tayar C, Laurent A, Karoui M, Loriau J, Cherqui D. (2007) Laparoscopic liver resection for benign disease. *Arch Surg* 142:1188–1193. discussion 93.
 169. Chaib E, Gama-Rodrigues J, Ribeiro MA, Jr, Herman P, Saad WA. (2007) Hepatic adenoma. Timing for surgery. *Hepatogastroenterology* 54:1382–1387.
 170. Dagher I, Proske JM, Carloni A, Richa H, Tranchart H, Franco D. (2007) Laparoscopic liver resection: results for 70 patients. *Surg Endosc* 21:619–624.
 171. Hompes D, Aerts R, Penninckx F, Topal B. (2007) Laparoscopic liver resection using radiofrequency coagulation. *Surg Endosc* 21:175–180.
 172. Ibrahim S, Chen CL, Wang SH, Lin CC, Yang CH, Yong CC *et al.* (2007) Liver resection for benign liver tumors: indications and outcome. *Am J Surg* 193:5–9.
 173. Koffron AJ, Auffenberg G, Kung R, Abecassis M. (2007) Evaluation of 300 minimally invasive liver resections at a single institution: less is more. *Ann Surg* 246:385–392. discussion 92–94.
 174. Nissen NN, Grewal N, Lee J, Nawabi A, Korman J. (2007) Completely laparoscopic nonanatomic hepatic resection using saline-cooled cautery and hydrodissection. *Am Surg* 73:987–990.
 175. Poultides G, Brown M, Orlando R, 3rd. (2007) Hand-assisted laparoscopic management of liver tumors. *Surg Endosc* 21:1275–1279.
 176. Reddy SK, Kishnani PS, Sullivan JA, Koeberl DD, Desai DM, Skinner MA *et al.* (2007) Resection of hepatocellular adenoma in patients with glycogen storage disease type Ia. *J Hepatol* 47:658–663.
 177. Teeuwen PH, Ruers TJ, Wobbes T. (2007) [Hepatocellular adenoma, a tumour particularly seen in mostly young women]. *Ned Tijdschr Geneesk* 151:1321–1324.
 178. Balaa FK, Gamblin TC, Tsung A, Marsh JW, Geller DA. (2008) Right hepatic lobectomy using the staple technique in 101 patients. *J Gastrointest Surg* 12:338–343.
 179. Buell JF, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV *et al.* (2008) Experience with more than 500 minimally invasive hepatic procedures. *Ann Surg* 248:475–486.
 180. Feng ZQ, Huang ZQ, Xu LN, Liu R, Zhang AQ, Huang XQ *et al.* (2008) Liver resection for benign hepatic lesions: a retrospective analysis of 827 consecutive cases. *World J Gastroenterol* 14:7247–7251.
 181. Machado MA, Makdissi FF, Galvao FH, Machado MC. (2008) Intrahepatic Glissonian approach for laparoscopic right segmental liver resections. *Am J Surg* 196:e38–e42.
 182. Petri A, Hohn J, Kokai EL, Savanya GK, Lazar G. (2008) Surgery of

- benign liver tumors: indications for treatment: twenty years' experience. *Hepatogastroenterology* 55:592–595.
183. Popescu I, Ciurea S, Romanescu D, Boros M. (2008) Isolated resection of the caudate lobe: indications, technique and results. *Hepatogastroenterology* 55:831–835.
 184. Pulitano C, Catena M, Arru M, Guzzetti E, Comotti L, Ferla G *et al.* (2008) Laparoscopic liver resection without portal clamping: a prospective evaluation. *Surg Endosc* 22:2196–2200.
 185. Spencer L, Metcalfe MS, Strickland AD, Elsey EJ, Robertson GS, Lloyd DM. (2008) Lessons from laparoscopic liver surgery: a nine-year case series. *HPB Surg* 2008:458137.
 186. Troisi R, Montalti R, Smeets P, Van Huysse J, Van Vlierberghe H, Colle I *et al.* (2008) The value of laparoscopic liver surgery for solid benign hepatic tumors. *Surg Endosc* 22:38–44.
 187. Abu Hilal M, Underwood T, Taylor MG, Hamdan K, Elberm H, Pearce NW. (2010) Bleeding and hemostasis in laparoscopic liver surgery. *Surg Endosc* 24:572–577.
 188. Al Awad-Jibara A, Chirinos Vargas JR, Baena SJ, Pirela-Finol CA, Brea-Andrade AF, Yajure-Perozo ME. (2009) [Laparoscopic hepatectomy in benign solid tumor: case report]. *Cir Cir* 77:223–227.
 189. Bryant R, Laurent A, Tayar C, Cherqui D. (2009) Laparoscopic liver resection-understanding its role in current practice: the Henri Mondor Hospital experience. *Ann Surg* 250:103–111.
 190. Ito K, Ito H, Are C, Allen PJ, Fong Y, Dematteo RP *et al.* (2009) Laparoscopic versus open liver resection: a matched-pair case control study. *J Gastrointest Surg* 13:2276–2283.
 191. Machado MA, Makdissi FF, Surjan RC, Herman P, Teixeira AR, MC CM. (2009) Laparoscopic resection of left liver segments using the intra-hepatic Glissonian approach. *Surg Endosc* 23:2615–2619.
 192. Skalicky T, Treska V, Sutnar A, Liska V, Molacek J, Mirka H *et al.* (2009) [Surgical treatment of benign liver tumours – indications and results]. *Zentralbl Chir* 134:141–144.
 193. Tomus C, Iancu C, Bala O, Graur F, Furcea L, Zaharie F *et al.* (2009) [Liver resection for benign hepatic lesion: mortality, morbidity and risk factors for postoperative complications]. *Chirurgia (Bucur)* 104:275–280.
 194. Watkins J, Balabaud C, Bioulac-Sage P, Sharma D, Dhillion A. (2009) Hepatocellular adenoma in advanced-stage fatty liver disease. *Eur J Gastroenterol Hepatol* 21:932–936.
 195. Korula J, Yellin A, Kanel G, Campofiori G, Nichols P. (1991) Hepatocellular carcinoma coexisting with hepatic adenoma. Incidental discovery after long-term oral contraceptive use. *West J Med* 155:416–418.
 196. Ferrell LD. (1993) Hepatocellular carcinoma arising in a focus of multilobular adenoma. A case report. *Am J Surg Pathol* 17:525–529.
 197. Herman P, Machado MA, Volpe P, Pugliese V, Vianna MR, Bacchella T *et al.* (1994) [Transformation of hepatic adenoma into hepatocellular carcinoma in patients with prolonged use of oral contraceptives]. *Rev Hosp Clin Fac Med Sao Paulo* 49:30–33.
 198. Perret AG, Mosnier JF, Porcheron J, Cuilleron M, Berthouix P, Boucheron S *et al.* (1996) Role of oral contraceptives in the growth of a multilobular adenoma associated with a hepatocellular carcinoma in a young woman. *J Hepatol* 25:976–979.
 199. Scott FR, el-Refaie A, More L, Scheuer PJ, Dhillion AP. (1996) Hepatocellular carcinoma arising in an adenoma: value of QBend 10 immunostaining in diagnosis of liver cell carcinoma. *Histopathology* 28:472–474.
 200. Burri E, Steuerwald M, Cathomas G, Mentha G, Majno P, Rubbia-Brandt L *et al.* (2006) Hepatocellular carcinoma in a liver-cell adenoma within a non-cirrhotic liver. *Eur J Gastroenterol Hepatol* 18:437–441.